**DRUG NAMES TO KNOW/RECOGNIZE**

* **Inulin**
* **Penicillin**
* **Probenecid**
* **Acetaminophen**

**ELIMINATION OF DRUG: EXCRETION OBJECTIVES**

1. **Describe the major processes by which drugs are handled at various sites long the nephron**
2. **Recognize that many different drug transporters play key roles in eliminating drugs from the body.**
3. **Describe active secretion of cationic drugs in the proximal tubule and how this transepithelial transport is achieved by facilitated diffusion in the basolateral membrane and electroneutral exchange in the luminal membarne.**
4. **Describe active secretion of anionic drugs in the proximal tubule and how this transepithelial transport is achieved by secondary active transport in the basolateral membrane and ATP driven ABC transporters in the luminal membrane.**
5. **Describe the four major characteristics of a drug that allows one to predict how it will be handled by the kidneys.**
6. **Describe the handling of inulin, penicillin and probenecid by the kidney.**
7. **Recognize that in some cases the properties of a drug prevent efficient elimination by the kidney**
8. **Describe the role drug metabolism plays in modifying properties of drugs to facilitate elimination by the kidney and or feces**
9. **Identify major sites of drug biotransformation, but recognize it also occurs at other sites too.**
10. **Describe the two phases of drug biotransformation that often work in tandem and their general characterization as non-synthetic and synthetic processes.**
11. **Describe the major pathways for drug biotransformation.**
12. **Recognize that oxidation by cytochrome P450 enzymes is the most common phase I process and glucuronidation the most common phase II process.** 
    1. **Phase I --often produces active metabolites** 
       1. **OXIDATION REACTIONS CYTOCHROME P450 SYSTEM (in sER🡪 microsomes!)** 
          1. **Hydroxylation** of aliphatic and aromatic carbons—addition of a hydroxyl group to the drug
             1. Ibuprofen
             2. S-warfarin—CYP2C9 plays an important role in determining the in vivo activity of this drug
          2. **Deamination** and N**-dealkylation**—carbons attached to nitrogen atoms can be oxidized and severing of the C-N bond producing an ammine or ammonia and a keto compound
             1. α-OH-amphetamine
             2. Theophylline (asthma)—inactivated by demethylation to 3-methyl-xanthine
          3. **O**-**Dealkylation**—oxidation of a carbon attached to the oxygen in an ether (R-O-R) severs the C-O bond producing an alcohol and a keto compound
             1. Codeine (opiod)🡪 converted to morphine (**more potent** opiod analgesic) by removing a methyl group
          4. **N-oxidation and S-oxidation—**nitrogen or sulfur atoms can be directly oxidized by adding an oxygen
             1. **ACETAMINOPHEN (only 1-2% of biotransformation of this drug)**

The product of N-oxidation (CYP2E1, CYP3A4) loses water to produce a toxic produce🡪 NAPQI

* + - * 1. Omeprazole (PPI—to inhibit gastric secretions) –used CYP3A4
    1. **HYDROLYSIS REACTIONS**
       1. **Epoxide Hydrolase (EH)—**CYP’s can produce epoxides which are reactive and **EH** converts the epoxide to a diol
          1. Cabamazepine (antiepileptic drug—drug needs to go to brain so good PC)
       2. **Esterase—carboxylesterases (CES)—hydrolyze esters to an acid and an alcohol** 
          1. Found in the ER and cytosol of many cells, in the blood, and plasma, etc
          2. Methylphenidate (Ritalin)—inactivated by an esterase
          3. Latanoprost (Xalantan—treats glaucoma)---**activated**  by an esterase in the cornea of the eye
       3. **Amidase—hydrolyzes amides to the amine and an acid** 
          1. Lidocain (local anesthetic)—inactivated by amidase –activated by N-dealkylation in the liver and then inactivaded by an amidase in the liver
  1. **Phase II (conjugation reactions)** 
     1. Adds a group to the drug or metabolite and leads to inactivation except in morphine and minoxidil
     2. Usually ↓ PC
     3. **Glucuronidation (UGT’s)—adds glucuronic acid \*\*MOST IMPORTANT CONJUGATION REACTION**
        1. Glucuronate is transferred by UDP-glucuronic acid by **UDP-glucuronosyltransferases (UGTs)**
        2. Many recipient groups on drugs
        3. UGT’s are in ER (mircosomes) in most tissues but are most abundant in the **liver and GI tract**
           1. Glucuronidation commonly occurs after oxidation so it is beneficial to have it also occur in the ER in microsomes
        4. Effects of glucuronidation
           1. ↑ water solubility🡪 less binding to albumin and more filtration in the glomerulus
           2. provides negative charge🡪 product is a substrate for anion pump (secretion mechanisms) in the kidney and liver & cannot undergo non-ionic reabsorption in the kidneys
        5. UGT1 and UGT2
           1. UGT1A1 is important for conjugation of bilirubin

Mutations🡪 jaundice

Gilbert’s Syndrome—plasma bilirubin ↑ 60-70%, higher risk of drug interations. Most common cause is a promoter mutation UGT1A1\*28

Crigler Najjar Sundrome I—rare no active UGT1A1, no bilirubin conjugation, early childhood death

* + - * 1. UGT2—more important for endogenous substrates (steroids)
      1. **ACETAMINOPHEN (65% is inactivated by glucuronidation in the liver)** 
         1. This make acetaminophen more water soluble b/c is added a sugar🡪 ↑ water solubility b/c sugar is also hydrophilic (poor PC) 🡪 means ↓ bound to plasma proteins🡪 ↓ drug can get into cells (poor PC) 🡪 more of the drug is now filtered and has charge (poor PC) so good secretion substrate
    1. **Sulfation (SULTS)—adds sulfate**
       1. Adds sulfate from PAPS primarily to Aromatic-OH but sometimes to R-OH or R-NH2
       2. Humans have many families of SULTS (1, 2, 4 and 6)🡪found in liver, GI tract, skin etc.
       3. Endogenous substrates—hormones: estrogen, DHEA, cholesterol, iodothyronine, catecholamines
       4. Xenobiotics—SULT1 most important for these
          1. SULT1A1—liver
          2. SULT1B1—intestine
       5. **ACETAMINOPHEN (30% inactivated by sulfation)** 
          1. **PAPS adds sulfate group on the Aromatic-OH**
       6. **MINOXIDIL (rogaine)—**a prodrug activated by sulfation is a vasodilator for treating hypertension and a topical therapy for baldness
    2. **Glutathione Conjugation** 
       1. GSH reacts with electrophilic substances that may cause oxidative damage to cell
       2. Glutathione is a tripeptide containing Glu-Cys-Gly,--has a reactive thiol group
       3. GSH oxidation by electrophils can produce an oxidized dimer with S-S bridge (GSSG)
       4. GSSG is reduced by glutathione Reductase (uses NADPH generated by the pentose phosphate pathway
       5. Conjugation is mediated by glutathione-S-transferases (GST)
          1. Microsomal GST mainly for endogenous substrances
          2. Cytosolic GST mainly for xenobiotics and drugs
          3. GST and GSH protect cell proteins
       6. **ACETAMINOPHEN**
          1. Oxidation by CYP2E1 generates NAPQI (toxic)🡪 then conjugation with glutathione produces a non-toxic metabolite

NAPQI likes to react with –SH groups in protein in cells and kill them

In the liver can kill enough cells to cause liver damage and a person can die

* + - * 1. The glutamate and glycine are subsequently removed (these were on glutathione) leaving only cysteine🡪cysteine is then N-acetylated leaving a mercapturic acid
        2. Toxic overdoses of acetaminophen deplete glutathione and liver toxicity can be minimized by prompt treatment with N-acetylcysteine (antidote)
    1. **N-acetylation (a lot less common than the others—makes products that are LESS WATER SOLUBLE)** 
       1. Transfer of an acetyl group from acetyl-CoA to an aromatic amine or hydrazine group
       2. Polarity of the drug is decreased
       3. Catalyzed by NAT’s
          1. NAT1—ubiquitous
          2. NAT2—GI tract and liver
       4. Hydralazine (vasodilator used to tx HTN) is inactivated by N-acetylation (has a high 1st pass metabolism by acetylation)
          1. Slow acetylators (35% bioavailability vs. 16% for fast) have ↑ risk of side effects such as SLE-like syndrome (no renal damage)
    2. **Methylation (a lot less common than the others—makes products that are LESS WATER SOLUBLE)**
       1. Methyl group transferred from SAM to O, N. or S atoms
       2. Methylation ↓ drug polarity
       3. Substrate specificity is generally high
          1. N-methyltransferases
          2. COMT
          3. POMT
          4. TMT
          5. TPMT—transfers methyl to 6-mercaptopurine

Azathioprine (prodrug)🡪 6-mercaptopurine (6-MP)

drug for immune suppression, RA, IBD

6-MP is cytotoxic 🡪 is metabolized to 6-thioguanine nts which are incorporated into DNA and inhibit replication

without TPMT the patients would have severe toxicity (so don’t prescribe patients with TPMT deficiencies these drugs)

1. **Recognize that biotransformation usually results in drug inactivation and accelerated elimination, but that in some cases biotransformation can be exploited to activate a drug or may generate a toxic product.**
2. **Describe metabolism of acetaminophen to illustrate phase 1 and phase 2 biotransformation and recognize the significance of this metabolism**
3. **Describe the process of drug handling in the hepatocytes including the role of transporters in the hepatocyte sinusoidal membranes in taking up drugs for metabolism and the role of transporters in the sinusoidal and canalicular membranes in determining the final destination of these drugs and metabolites.** 
   1. Blood flows from the HPV & HA to the central vein
      1. Drugs are brought directly from the GI tract via the HPV and from the rest of the body by the HA
      2. Liver cells lining sinusoids extract drugs, by drug transporters similar to those in the kidney and by passive diffusion
   2. Parent drugs or drug metabolized in the liver are then transported out of the cells via one of two pathways
      1. Back into the systemic circulation where they may be excreted by the kidney
      2. Into the bile canaliculus and on to the gall bladder for release into the small intestine via the bile duct with the bile—**biliary secretion**
   3. Transporters in the hepatocyte
      1. Entry from the blood is mediated by SLC transporters OATs and OATps and OCTs in the **sinusoidal membrane**
         1. Driven by membrane protential generated by the NaK ATPase pump
      2. Exit into bile is mediated by ABC transporters (P-gp/MDR1, MRP2, BRCP) in the **canalicular membrane** 
         1. Driven by ATP hydrolysis
         2. MRP2—acetaminophen-glucuronide/sulfate
      3. Exit into blood is mediated by ABC transporters (MRP1, 3, & 4 in the **sinusoidal membrane)**
         1. Driven by ATP hydrolysis
         2. Ex: MRP3 transports acetaminophine-glucuronide back into blood
4. **Describe biliary excretion of drugs and enterohepatic cycling of drugs (and drug interactions)** 
   1. A drug or its metabolite that undergoes biliary excretion (may not be actually excreted from the body) into the GI tract follows one of two pathways depending on its PC
      1. Poor PC🡪 remain in the GI tract and be excreted in the feces
      2. Favorable PC🡪 will be reabsorbed via passive diffusion and pass back to the liver via the blood
      3. Drug that has been conjugated with glucuronic acid has **very unfavorable** PC but bacteria that reside in the colon can remove the glucuronic acid and release the drug🡪 if the realeased drug has a favorable PC it will be reabsorbed by passive diffusion and pass back to the liver and be reconjugated and passed back into the bile (ENTEROHEPTATIC CYCLING)
         1. Most drugs that undergo enteroheptic cycling are ultimately eliminated by the kidney
   2. **Ex:** birthcontrol---cycling is depend on bacteria. Birthcontrol undergoes sulfation and glucuronidation and cycles over and over. If you kill the bacteria you ↓ enterohepatic cycling and ↓ the time birth control is in the body which is why a person who is taking antibiotics has an ↑ risk of getting pregnant.
      1. Some bacteria promote enterohepatic cycling so when you kill them with a broad spectrum antibiotic (especially those in the GI tract) you significantly ↓ the ½ life of other antibiotics
      2. Non-absorbable polymers can also ↓ enterohepatic cycling
         1. Cholestyramine, fiber
            1. Cholestyramine is a resin that binds things with negative charge and bile acids🡪prevents enterohepatic cycling of bile acids b/c ↓ in bile acids being reabsorbed through GI means liver need to compensate by pulling out more cholesterol from blood to make more bile acids🡪 results in ↓ plasma cholesterol